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EXAMINER	
HOGUE, C	
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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire three(3) month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892. ✓
2. ☒ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449. ✓
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 1-56 are pending in the application.

Of the above, claims _____ are withdrawn from consideration.

2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-56 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

PTOL-326 (Rev. 2-95)

EXAMINER'S ACTION

Part III DETAILED ACTION

1. The drawings are objected to because (1) the labels on the x-axis of Figure 10 are not adequetely spaced and (2) the lettering in Figure 18 is not legible. Correction is required.

2. The disclosure is objected to because of the following informalities: Row 3 of Table 6 on pg. 25 in the "Route" column should read "iv" instead of "in". Appropriate correction is required.

3. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure.

Applicant's invention is directed toward a method of immunizing against various pathogens including influenza,

rotavirus, HIV and SIV. Specifically, the invention encompasses immunizing an animal with a DNA transcription unit in order to elicit a humoral and/or a cell-mediated immune response. Several working examples are given in which mice, chickens, and ferrets were immunized with DNA encoding the influenza hemagglutinin types H1 and H7. Various routes of administration and different promoters of retroviral and nonretroviral origin were used in these experiments. Other experiments in mice demonstrated that antibody titers to rotavirus, HIV, and SIV could be achieved with DNA encoding various epitopes of these pathogens.

There is, however, a lack of guidance given regarding the composition, dosage and administration regimens that humans would require for protection for the following reasons: 1) The data cited by the applicant also lends itself to a high degree of unpredictability. 2) Table 2 illustrates the unpredictability in the type of response achieved by the influenza vaccine. Because of the variability of these results it would be difficult for one skilled in the art to determine the appropriate variables suitable for use in humans (route of administration, dosages, promoters, boosters, etc.). 3) Due to the recognized unpredictability in the duration of expression, DNA stability and the complexity of the immune system in the diverse types of animals encompassed by the claims, undue experimentation would be required to practice the claimed invention.

Furthermore, the specification lends itself to high degree of unpredictability because it utilizes mouse and other animal experimentation as a predictor of an effective vaccine in all vertebrates. The extrapolation of animal studies in general as they relate to gene transfer in humans should be done with caution. Ledley [Human Gene Therapy, 2:77-83 (1991)] on page 79 under Considerations of Animal Models for Somatic Gene Therapy discusses the relevance of animal experiments to assess gene transfer. Although directed to gene transfer using retroviral vectors, the discussion is relevant in understanding the limits of animal experimentation in predicting outcomes of gene transfer and expression in humans:

> While animal experiments are useful for assessing specific aspects of gene transfer, there is no data explicitly supporting the contention that animal experiments can presage the outcome, efficacy, or safety of human applications. The details of anatomy, cell biology, genetics, and immunology of other species do not duplicate the vicissitudes of human biology ... Controlled data justifying the utility of animal models could be obtained by judicious clinical trials performed in conjunction with ongoing animal experiments. Such studies could ultimately reduce the number, extent, and danger of human investigations by determining how to obtain meaningful data from animal experiments. Without a baseline of information from human subjects, the current generation of animal experiments may be unnecessary and uniformative, and future clinical trials may subject patients to the same risks that animal experiments are designed to avoid.

In particular, regarding HIV and SIV, the use of animal models is discussed by Haynes [Science, 260:1279-1286 (1993)] on page 1280, first column:

> Animal Models. In spite of an extraordinary amount of work in search of an animal model for human AIDS, no animal model exactly mirrors human HIV infection. In general, current animal models of HIV or simian immunodeficiency virus (SIV) infection either do not develop AIDS symptoms, do not develop immune responses analogous to human anti-HIV T and B cell responses, or involve the use of endangered species such as chimpanzees. Thus, many important scientific questions of HIV vaccine development must be answered in human clinical trials. (references omitted)

Further, Haynes discusses on page 1280, first column:

> Correlates of Protective Immunity Against HIV. Because of an animal model of human AIDS and because a cohort of individuals naturally resistant to HIV infection is not available, the immune correlates of protection against HIV are not known. For those working on a preventive HIV vaccine, lack of these critical data has forced the design of experimental immunogens that induce some or all of the types of immune responses that are surmised, but not yet known, to be protective against HIV (Table 1). (references omitted)

Haynes cites several references which "suggested that cellular immune responses may be protective against HIV infection." However, the ability to generate a protective CTL response is still questionable. After infection of individuals with most viruses, a CTL response typically exists only transiently, but individuals infected with HIV-1 have persistent circulating CTLs. The art has shown that structural, enzymatic and regulatory proteins from HIV-1 all can serve as CTL targets. But, as concluded by Hoffenbach et al. [The Journal of Immunology, 142(2):452-462 (1989)] on page 459, "no clear correlation exists at present between the presence of HIV-specific CTL and resistance to progression toward AIDS."

Therefore, it is clear that despite an initial strong CTL response to HIV, patients will eventually develop AIDS. Consequently, it is unpredictable as to whether stimulation of an HIV-specific antibody or HIV-specific CTL response by applicant's methods would result in a beneficial, protective immune response to prevent HIV infection. Interestingly, Butini et al. [Journal or Cellular Biochemistry, Suppl. 18B:147, abstract J306 (1994)] compares the CTL activity in two patients with HIV infection. The patient with high HIV-specific CTL activity had rapidly progressive disease, while the patient with no CTL activity was found to have no progression of immunodeficiency disease. Evidently, the presence of high levels of circulating HIV-specific CTLs cannot by directly extrapolated to inhibition of viral spread.

Clearly, applicant's methods and compositions as claimed are not supported by evidence that is demonstrative or predictive of immunoprotection against rotavirus, HIV or SIV. Furthermore, applicant's methods and compositions are not indicative of protection against influenza in animals other than chickens, mice and ferrets. Since applicant's have not demonstrated a consistent and reproducible stimulation of antibody formation, or CTL activity against certain antigens, the skilled artisan would not accept these responses as correlative of a protective immune

response against the corresponding pathogen for the scope of the invention as claimed.

The skilled artisan would not be able to practice a method of immunizing an individual with the expectation of eliciting a protective immune response to SIV or HIV using the applicant's method. In unpredictable areas of endeavor, the *in vitro* or *in vivo* experimental data must be generally recognized by those of ordinary skill in the art as being reasonably predictive of success in practicing the claimed invention. Insofar as HIV immunity is concerned, as discussed above, Haynes indicates that there is no animal model of HIV which mimics the disease or course of infection. Furthermore, Hoffenbach et al. questions the benefit of a CTL response in preventing or slowing HIV infection.

Consequently, the specification is non-enabling in view of the acknowledged complex and unpredictable nature of the subject matter, the lack of working examples which are correlatable to the claimed immunization method, the lack of guidance provided as to selection of the essential combination of parameters which would result in an effective immunizing composition, and the breadth of the claims.

4. Claims 1-56 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the

specification. Specifically, claims 45-49 and 53-56 are not enabled in the specification. Nowhere in the specification does the applicant discuss or provide examples of immunizing with multiple DNA transcription units encoding proteins from the influenza virus. Although one example of immunizating with multiple transcription units in the case of HIV is given, it not apparent to the examiner that this example is representative of all the possible permutations that are encompassed by the claims.

5. Claims 1, 16, 17, 32, 44, and 52 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is not clear from these claims whether or not the DNA transcription unit is expressed in the cells of the vertebrate. It is necessary to include this limitation in the claims otherwise it is not clear how the antigen would induce an immune response.

6. Claims 4 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The use of the word "capable" renders this claim vague and indefinite. It is not clear whether or not

a protective immune response is induced. If not, then what purpose would the method serve?

7. Claim 53 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "one or more" renders this claim vague and indefinite. The composition of the vector is not clear from this description.

8. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

9. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 86 S.Ct. 684, 15 L.Ed. 2nd 545 (1966), 148 USPQ

459, that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103 are summarized as follows:

1. Determining the scope and contents of the prior art;
2. Ascertaining the differences between the prior art and the claims at issue; and
3. Resolving the level of ordinary skill in the pertinent art.

10. Claims 1-7, 10-14, 16-22, 24-26, 29-38, 41-49, and 51-56 are rejected under 35 U.S.C. § 103 as being unpatentable over Felgner (WO 90/11092) in view of Huylebroeck et al [Technological Advances in Vaccine Development, 1988].

Felgner teaches:

> a method for immunizing a vertebrate, comprising the steps of obtaining a preparation comprising an expressible polynucleotide coding for an immunogenic translation product, and introducing the preparation into a vertebrate wherein the translation product of the polynucleotide is formed by a cell of the vertebrate, which elicits an immune response against the immunogen.

Felgner indicates on page 14 that his method may be used to selectively elicit a humoral and/or cellular immune response. On page 11, he states that the polynucleotide sequence may also include a promoter sequence. This statement is further qualified on page 19, where Felgner mentions various promoters of retroviral and nonretroviral origin commonly used in the art.

On page 14, Felgner teaches that the immunogenic peptide can be associated with a virus. He specifically teaches two examples

on pages 55-57, in which a polynucleotide encoding an HIV protein (gp120 and nef) is introduced into a mammal resulting in an immune response capable of protection.

Felgner also teaches several routes of administration including intravenous, intramuscular, intraperitoneal, intradermal, and subcutaneous. Mucosal administration is taught on page 43:

> The parenteral route of injection into the interstitial space of tissues is preferred, although other parenteral routes, such as inhalation of an aerosol formulation, may be required in specific administration, as for example to the mucous membranes of the nose, throat, bronchial tissues or lungs.

Felgner does not specifically describe a method of immunizing a vertebrate with a transcription unit encoding an influenza antigen. However, Huylebroeck describes viral delivery systems in which DNA encoding the influenza viral hemagglutinin is incorporated into a SV40 plasmid and subsequently expressed in monkey cells (page 279, Figure 1, Table 1). The polypeptides produced in this fashion were then capable of eliciting a protective immune response in mice.

Given the importance of developing better vaccines for the influenza virus and the importance of the hemagglutinin protein in the generation of protective immune responses, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Felgner on delivery of polynucleotides to vertebrate tissues, with the

teachings of Huylebroeck on the construction of expression vectors encoding the influenza viral hemagglutinin, to include the DNA encoding viral hemagglutinin from influenza in a DNA transcription unit. A method of immunizing an animal including humans with the DNA transcription unit would have also been obvious, with the expectation, barring evidence to the contrary, that the DNA transcription unit would avoid the need to purify the HA antigen before use and the transcription unit would also generate humoral and cell-mediated immune responses when administered *in vivo*.

Finally, it is the examiner's position that it is well within the level of those skilled in the art to immunize with more than one DNA transcription unit to provide protection against different epitopes present during the course of an infection. Therefore it would have been obvious to a person of ordinary skill in the art at the time the invention was made, how to make and use applicant's claimed invention.

11. Claims 15 and 23 are rejected under 35 U.S.C. § 103 as being unpatentable over Felgner (WO 90/11092) in view of Tang [Nature, 356:152-154 (1992)].

Felgner teaches a method of immunization using DNA transcription units as outlined in rejection #7 of this office

action. However, Felgner does not teach the use of a gene gun or microsphere encapsulation to deliver the DNA transcription unit.

Tang teaches a method of immunizing with DNA by delivering DNA-coated gold microprojectiles directly into cells of a living animal.

Therefore, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to use the methods described by Felgner with the delivery mechansim of Tang, due to the simplicity with which the DNA can be delivered to the animal, with the expectation of elicting a more potent immune response demonstrated by the gene gun mechanism.

12. Claims 8, 27, 39 are rejected under 35 U.S.C. § 103 as being unpatentable over Felgner (WO 90/11092) in view of Both (WO 89/07140).

Felgner teaches a method of immunization using DNA transcription units as outlined in rejection #7 of this office action. However, Felgner does not teach an immune response against a rotavirus antigen.

Both teaches a method for constructing a vector containing the VP7 rotavirus capsid protein and subsequent expression in an animal cell line. The gene product isolated using this method is then used to immunize a vertebrate.

Therefore, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to use the methods described by Felgner with the concept of Both to include the VP7 rotavirus protein in a vector capable of producing an immunogenic protein in an animal cell, recognizing that by directly administering the vector to the animal there would be no need to isolate the gene product before immunization.

13. Claims 9, 28, 40, 50 are rejected under 35 U.S.C. § 103 as being unpatentable over Felgner (WO 90/11092) in view of Haynes (WO 93/17706).

Felgner teaches a method of immunization using DNA transcription units as outlined in rejection #7 of this office action. However, Felgner does not teach an immune response against a simian immunodeficiency virus antigen.

Haynes teaches a method of immunizing with a genetic construction encoding antigenic determinants of an immunodeficiency virus, specifically SIV and HIV (page 9, lines 28-29).

Therefore, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to combine the methods described by Felgner with the genes encoding the simian immunodeficiency virus described by Haynes,

recognizing the urgent need for a vaccine against immunodeficiency viruses.

14. 35 U.S.C. § 101 reads as follows:

> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

15. Claims 17-18, 21, 24-26, and 30-31 are provisionally rejected under 35 U.S.C. § 101 as claiming the same invention as that of claims 11-12, 13, 14, 22-23, and 17-18 of copending application Serial No. 08/009,833. This is a *provisional* double patenting rejection since the conflicting claims have not in fact been patented. Claims 17-18, 21, 24-26, and 30-31 of applicant are identical in scope to Claims 11-12, 13, 14, 22-23, and 17-18 of application Serial No. 08/009,833.

16. Claims 1-16, 19-20, 22-23, 27-29, and 32-56 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-2, 4, 7-14, and 17-24 of copending application Serial No. 08/009,833 in view of Ulmer et al. [Science, 259:1745-1749 (1993)]. Although the conflicting claims are not identical, they are not patentably distinct from each other because they differ only in scope from the prior application. The use of the claimed method for immunizing against other viral infections would be obvious to one of ordinary skill in the art. Also, the use of different routes of administration is well within the level of one skilled in the art.

Claims 3, 19, and 35 are obvious variations of the prior claims, in that retroviral promoter regions are well known in the art. The use of a retroviral promoter is documented in Ulmer et

al. in which a Rous sarcoma virus (RSV) promoter was used to immunize mice against influenza.

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

17. Claims 17-18, 21, 24-26, and 30-31 are provisionally rejected under 35 U.S.C. § 102(e) as being anticipated by copending application Serial No. 08/009,833.

Copending application Serial No. 08/009,833 has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the copending application, it would constitute prior art under 35 U.S.C. § 102(e) if patented. This provisional rejection under 35 U.S.C. § 102(e) is based upon a presumption of future patenting of the conflicting copending application. Application 08/009,833 discloses and claims an identical invention as that of applicant.

> This provisional rejection under section 102(e) might be overcome either by a showing under 37 C.F.R. § 1.132 that any unclaimed invention disclosed in the copending application was derived from the inventor of this application and is thus not the invention "by another", or by a showing of a date of invention of any unclaimed subject matter prior to the effective U.S. filing date of the copending application under 37 C.F.R. § 1.131.

18. Claims 1-16, 19-20, 22-23, 27-29, and 32-56 are provisionally rejected under 35 U.S.C. § 103 as being obvious over copending application Serial No. 08/009,833.

Application 08/009,833 discloses an invention identical to applicant's claimed invention as in the previous rejection. However, Claims 1-16, 19-20, 22-23, 27-29, and 32-56 are obvious variations of application 08/009,833. The use of the claimed method of 08/009,833 for immunizing against other viral infections and the use of a retroviral promoter would be obvious to one of ordinary skill in the art. Also, the use of different routes of administration is well within the level of one skilled in the art.

Copending application Serial No. 08/009,833 has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the copending application, it would constitute prior art under 35 U.S.C. § 102(e) if patented. This provisional rejection under 35 U.S.C. § 103 is based upon a presumption of future patenting of the conflicting application.

This provisional rejection might be overcome either by a showing under 37 C.F.R. § 1.132 that any unclaimed invention disclosed in the copending application was derived from the inventor of this application and is thus not the invention "by another", or by a showing of a date of invention prior to the effective U.S. filing date of the copending application under 37 C.F.R. § 1.131.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to D. Curtis Hogue, Jr. whose telephone number is (703) 308-1083. The examiner can normally be reached on Monday-Friday from 7:30 a.m. to 4:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jackie Stone, can be reached on (703) 308-3153. The fax phone number for this Group is (703) 308-4312.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Christopher S.F. Low

D. Curtis Hogue, Jr.
August 3, 1995

CHRISTOPHER S. F. LOW
PRIMARY EXAMINER
GROUP 1800